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Active infective endocarditis: Clinical characteristics and factors related to hospital mortality

Carlo Rostagno[1], Gabriele Rosso[1], Francesco Puggelli[1], Sandro Gelsomino[2], Lucio Braconi[2], Gian Franco Montesi[2], Stefano Romagnoli[3], Pier Luigi Stefano[2], Gian Franco Gensini[1]

[1]Dipartimento Area Critica, Università di Firenze, Italy
[2]Cardiochirurgia AOU Careggi, Firenze, Italy
[3]Cardioanestesia, AOU Careggi, Firenze, Italy

Abstract

Background: *Little information exists on the clinical characteristics and factors related to hospital mortality in patients with active infective endocarditis referred for surgery.*

Methods: *Between January 1, 2003 and December 31, 2006, 86 patients (56 males, 30 females, mean age 59.2 years) with active infective endocarditis were referred to our Department (2.8% of overall hospitalizations). The relation of several clinical, laboratory and echocardiographic findings at admission with hospital mortality was evaluated.*

Results: *A native valve (NVE) was involved in 50/86; the other 30 had a prosthetic valve endocarditis (PVE). Six had pacemaker endocarditis. The aortic valve was involved more frequently than the mitral valve, both in NVE and PVE. The tricuspid valve was involved in four drug addicts; 51% of patients were in NYHA class III–IV. Staphylococci and streptococci were isolated in 69% of patients (39% vs 30%). Blood cultures were negative in 24%. Overall hospital mortality has been 11.6%. Two patients died before surgery, eight in the perioperative period. Hospital mortality was closely related to age, clinical and laboratory evidence of advanced septic condition (temperature > 38°C, leukocytosis and creatinine > 2.0 mg/dL) and hemodynamic impairment.*

Conclusions: *Active infective endocarditis is a significant cause of referral to heart surgery departments and hospital mortality is still > 10%. Clinical and laboratory parameters easily available at admission suggest that severe sepsis and/or hemodynamic impairment may be helpful in predicting the clinical outcome in this group of high risk patients.* (Cardiol J 2010; 17, 6: 566–573)

Key words: endocarditis, surgery, prognosis, echocardiography

Address for correspondence: Prof. Carlo Rostagno, Dipartimento Area Critica Università di Firenze, Viale Morgagni 85, 50134 Florence, Italy, tel: +390557947632, fax: 0557947617, e-mail: c.rostagno@katamail.com

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Introduction

Despite a better knowledge of predisposing factors [1–3], the availability of new antibiotics [4], and closer adherence to prophylaxis guidelines, infective endocarditis remains a not uncommon severe clinical condition which is associated with high hospital mortality [5]. Symptoms may be overlooked in the early phases of disease. A long time between the early clinical manifestations and definite diagnosis may allow severe valvular damage and hemodynamic impairment to occur and shorten long term survival [6]. Medical treatment alone is frequently ineffective in these patients and three month mortality usually exceeds 30% [7]. Surgery, even in the active phase of disease, has been shown to significantly improve prognosis [8]. The recent International Endocarditis-Prospective Cohort Study reported that surgery was associated with a 39% decrease in the risk of death in comparison to medical treatment [9]. IE patients referred for surgery are high risk patients. Hospital outcome is related to severity of hemodynamic impairment and/or septic condition [10]. The aim of our prospective study was to assess the clinical and echocardographic characteristics of patients with active infective endocarditis referred to a tertiary heart surgery center, and to investigate whether simple clinical, laboratory and echo criteria, readily available at hospital admission, could predict clinical outcome in this high risk group.

Methods

Study design

We included in our study 86 consecutive patients admitted between January 1, 2003 and December 31, 2006 for active infective endocarditis (IE) to the Heart Surgery Department of AOU Careggi, Florence, Italy, a tertiary heart surgery referral center serving a population > 1.5 million.

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee.

On admission to our department, patients underwent: accurate history collection, physical examination with particular attention to heart (functional capacity assessed according to NYHA classification), neurological findings, skin or ocular manifestations , history or clinical evidence of systemic embolism, assessment of vital signs, measurement of body temperature, electrocardiogram, and laboratory examinations (hemoglobin concentration, leukocyte count, serum creatinine). At least three samples for blood cultures were collected within 12 hours. Blood samples were initially processed by an automatic system (Bactec, BD) and incubated for five days. When, following incubation, a bottle became positive, it was processed on chocolate AGAR, blood AGAR and orientation AGAR. MIC was calculated for different antibiotics in relation to isolated micro organism. Transthoracic and transesophageal echocardiography were performed with a Sequoia Accuson instrument (Siemens Medical Solution, Mount View, California, USA). All examinations were performed by two senior echocardiographers adhering to American Society of Echocardiography (ASE) guidelines [11]. A diagnosis of endocarditis was made in patients with systemic symptoms of infective disease who fulfilled the major echocardiographic criteria for IE which was thereafter confirmed by surgery [12].

Particular care was taken to research the presence and location of vegetations and/or perivalvular spreading of the infective process (abscesses, fistulas etc.). Standard semi-quantitative method was used to assess the severity of regurgitation: absent, mild (< 2+) or moderate-severe (3+ – 4+). Left ventricular ejection fraction (LVEF) was evaluated using the area-length method.

Indications for surgery

Hemodynamic impairment associated with severe mitral or aortic valve regurgitation was the main indication for surgery in 48% of patients. In 15 patients, surgery was indicated for paravalvular spreading of the infection with abscesses (14 subjects, 92% in prosthetic valve endocarditis) in one patient for aortic to right atrium fistula. Large vegetations > 10 mm diameter (24%) and recurrent embolism were the other main indications for surgery. All patients underwent surgery within seven days after starting maximal antibiotic treatment, unless impairment of clinical conditions suggested an earlier solution.

Statistical analysis

The quantitative variables are shown as means and standard deviations. In case of not continuous parameters has been reported the frequency of distribution. The statistical analysis of clinical data was performed using Student's t test for continuous data, while for categorical variables the χ^2 test was employed. Statistical analysis of echocardiographic parameters was carried out by ANOVA test. A probability value < 0.05 was considered statistically significant.

Table 1. Characteristics of patients included in the study.

Patients (mean age ± SD)	
Overall (n = 86)	59.5 ± 16.1
Men (n = 56)	57.3 ± 15.8
Women (n = 30)	63.1 ± 16.8
Systolic blood pressure [mm Hg]	127 ± 23
Diastolic blood pressure [mm Hg]	68 ± 14
Heart rate [beats/min]	112 ± 9.5
Type of valve involvment:	
Native valve endocarditis	50
Prosthetic valve endocarditis	30
Pacemaker endocarditis	6
Valve involved:	
Mitral	28
Aortic	38
Tricuspid	4
Mitral + aortic	10
NYHA class	
IV	21
III	23
II	14
I	28
C-reactive protein [mg/L]	23.7 ± 6.6

Results

General characteristics of patients

In the period under investigation, 86 patients with definite diagnosis of active IE [7] were admitted to our Division (2.8% of overall hospital admissions); 63 patients (73%) were referred from primary and secondary hospitals, while the other 27% were admitted through the Emergency Department of our hospital.

The mean age of patients was 59.5 years (range 22–84). There were more men than women (56 to 30) but the women were significantly older (63.1 *vs* 57.5 years; p = 0.03; Table 1). Native valves were involved in 50 patients (native valve endocarditis — NVE), while in 30, prosthetic valves were affected (prosthetic valve endocarditis — PVE). Twelve had early PVE (onset of clinical manifestations within 12 months from previous valvular heart surgery), while in the other 18 cases, the time elapsed from previous surgery and the onset of symptoms averaged 8.5 years (late PVE). The remaining six patients had pacemaker endocarditis.

Clinical features and laboratory findings

The duration between the onset of symptoms and hospitalization had been < 30 days in 33 patients (38%), and between one and six months in another 38 of them. In the remaining 15 subjects, symptoms had lasted > six months before a definite diagnosis. At hospital admission, 51% of patients were in NYHA functional class III or IV (Table 1). Fifty-five patients had fever (64%). A body temperature > 38°C was found in 18 patients (17%). Anemia (defined as serum hemoglobin concentration < 12 g/dL) was observed in 62 patients. In 31 patients, hemoglobin concentration was lower than 10 g/dL. White blood cell count > 10,000/mm^3 was present in 30 patients; only nine showed values > 15.000/mm^3.

Renal function was significantly impaired (serum creatinine > 2 mg/dL) in nine patients, while in 11 patients serum creatinine ranged between 1.5 and 2 mg/dL. Clinical manifestations and/or instrumental evidence of peripheral embolism were detected in 38% of patients, while petechiae and hematuria were present in five and three subjects respectively. C-reactive protein (CRP) values are reported in Table 1.

Average heart rate, systolic and diastolic blood pressure are reported in Table 1. Only four patients had systolic pressure below 100 mm Hg. A heart rate above 100 beats per minute was recorded in 29% of subjects.

Organisms responsible for infective endocarditis

Blood cultures were positive in 63 of the 86 patients (73%). Staphylococci were the most frequent isolated micro organism (Table 2). Methicillin-resistant staphylococci were isolated in eight patients. Streptococci were isolated in 41% of subjects with positive blood cultures, while Gram-negative in five. Fungal endocarditis (candida parapsilosis) was found in one immunodeficient patient. We detail in Table 2 the different pathogens responsible for IE respectively in NVE, PVE and pacemaker endocarditis.

Blood cultures were negative in 23 patients. Almost all these patients had been referred from peripheral hospitals and already treated with empiric large spectrum antibiotic therapy. 'Culture negative' endocarditis was more frequently observed (15 out of 23) in patients with NVE.

Echocardiographic findings

Preserved left ventricular systolic function (LVEF > 50%) was found in 70% of patients. Left ventricular function was moderately depressed (LVEF between 35 and 50%) in 27%. Only three patients showed a severe functional impairment (LVEF < 30%).

Table 2. Causal organism in relation to type of infected valve or device.

Etiological agent	Native valves	Prosthetic valves	PM endocarditis	Total
Staphylococcus aureus	9 (18%)	7 (23%)	1 (17%)	17 (23%)
Staphyloccoccus epidermidis	3 (6%)	5 (17%)	3 (50%)	11 (13%)
Other staphylococci	2 (4%)	0 (0%)	1 (17%)	3 (4%)
Streptococcus faecalis	2 (4%)	5 (17%)	0 (0%)	7 (7%)
Streptococcus viridans	4 (8%)	0 (0%)	0 (0%)	4 (4%)
Other streptococci	12 (24%)	3 (10%)	0 (0%)	15 (18%)
Gram-negative	2 (4%)	3 (10%)	0 (0%)	5 (7%)
Candida	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Negative blood culture	15 (30%)	7 (23%)	1 (17%)	23 (27%)

PM — pacemaker

Table 3. Echocardiographic findings in native valve endocarditis.

Endocarditic process	Aortic	Mitral	Tricuspidal
Mitral regurgitation			
Mild (≤ 2+)	12	5	1
Moderate-severe (3+/4+)	9	22	1
Absent	8	0	2
Aortic regurgitation			
Mild (≤ 2+)	2	3	0
Moderate-severe (3+/4+)	23	11	0
Absent	4	13	4
Tricuspidal regurgitation			
Absent-mild	13	13	2
Moderate-severe	16	14	2

Table 4. Echocardiographic findings in prosthetic valve endocarditis.

Endocarditic process	Aortic	Mitral	Tricuspidal
Mitral regurgitation			
Mild (≤ 2+)	10	3	0
Moderate-severe (3+/4+)	6	3	0
Absent	3	5	0
Aortic regurgitation			
Mild (≤ 2+)	4	8	0
Moderate-severe (3+/4+)	13	0	0
Absent	2	3	0
Tricuspidal regurgitation			
Evident	8	10	0
Absent	11	1	0

Native valve endocarditis. Endocarditic process involved a single valve in 40 subjects (mitral valve 17, aortic valve 19, tricuspid valve 4). In the remaining ten patients, both aortic and mitral valve were affected by the infective process. In Table 3, echocardiographic findings are reported in detail. Moderate to severe mitral regurgitation was found in nine patients with isolated aortic endocarditis, suggesting severe hemodynamic impairment leading to mitral annular dilation. About 50% of patients had severe tricuspid regurgitation with pulmonary hypertension. Single or multiple valve vegetations (average diameter 9.2 mm, range 3 to 20 mm) were detected in 47 patients. In two patients, perforation of a cusp was the cause of severe aortic regurgitation. Only one case of aortic NVE was complicated by paravalvular abscess and required homograft replacement. A severe left ventricular (LV) dysfunction (LVEF < 35%) was found in only two patients, while in 13 LVEF was between 35 and 50%.

Prosthetic valve endocarditis (Table 4)

Prosthetic valvular infection involved aortic valve in 19 patients and mitral valve in 11. In both positions, the infective process more frequently involved biological than mechanical valves. However, this may relate only to the larger number of biological valves implanted in comparison to mechanical prostheses. Vegetations were detected in four patients with aortic biological prosthetic endocarditis, while a perivalvular abscess was detected in 12. In 13 out of 19 patients with aortic PVE we found moderate to severe aortic valvular regurgitation: a perivalvular leak was responsible for regurgita-

Table 5. Clinical outcome in relation to demographic and hemodynamic factors.

Parameter	Patients discharged alive (n = 76)	Patients died (n = 10)	t	p
Age [years]	58.1 ± 16.3	69.7 ± 10	2.194	0.03
Heart rate [bpm]	87 ± 19	105 ± 20	2.67	0.009
Systolic heart pressure [mm Hg]	127 ± 22	130 ± 23	0.384	0.710
Diastolic heart pressure [mm Hg]	67 ± 16	71 ± 16	0.69	0.492

Table 6. Clinical outcome in relation to echocardiographic parameters.

Parameter	Patients discharged alive (n = 76)	Patients died (n = 10)	χ^2	p
Left ventricular ejection fraction				
> 50%	56	1		
35–50%	18	5	25.7	< 0.0001
< 35%	2	4		
Aortic regurgitation				
3+ – 4+	36	2		
< 2+	30	5	1.93	0.37
0	20	3		
Mitral regurgitation				
3+ – 4+	32	3		
< 2+	26	4	0.57	0.77
0	18	3		

tion in six patients, while in the other seven valve regurgitation was related to damage and perforation of prosthetic valve leaflets. Mitral valve regurgitation was found in 22 patients. Left ventricular function was moderately depressed (LVEF 35–50%) in 30% of cases of PVE.

Pacemaker endocarditis

All six patients with pacemaker IE developed vegetations on ventricular and/or atrial electrodes. Five patients (83%) had a significant tricuspid regurgitation.

Hospital outcome

Mortality. Overall hospital mortality has been 11.6% (10 out of 86); mortality rose to 12.5% (10 out of 80) when patients with pacemaker endocarditis were excluded from the analysis. Two patients died before surgery and eight in the post-operative period. In one case, death occurred during surgery for rupture of atrioventricular sulcum. The other patients died within 30 days from intervention: three due to irreversible cardiogenic shock, three due to multiple systemic organ failure as a result of severe septic shock, and the last one for rupture of splenic artery mycotic aneurysm.

Clinical factors related to mortality. Age was related to higher hospital mortality. Patients who died were on average 11 years older than patients discharged alive (Table 5). Gender did not influence clinical outcome. We did not find any significant relation between survival and systolic and diastolic arterial blood pressure at admission, while a higher heart rate was related to an increased risk of death. Patients with evidence of LV dysfunction had a higher risk of death (nine of the ten patients who died had LVEF < 50%, compared to 30 out of 56 of those who survived; $p < 0{,}0001$; Table 6). Survival did not show any significant relation with the affected valve and was not related to native or prosthetic valve involvement. We failed to find any prognostic value of the degree of mitral or aortic regurgitation in both NVE and PVE or of the presence of complicated endocarditis (paravalvular abscesses or aortic — right atrium fistula).

Clinical and laboratory parameters related to severity of septic condition (such as higher tempera-

Table 7. Clinical outcome in relation to different clinical and laboratory parameters.

Parameter	Patients discharged alive (n = 76)	Patients died (n = 10)	χ^2	p
Temperature				
> 38°C	17	4		
37–38°C	34	6	2.51	0.01
< 37°C	25	0		
Total WBC				
> 15,000/mm^3	8	5		
10,000–15,000/mm^3	18	4	22.8	0.001
< 10,000/mm^3	50	1		
Hemoglobin				
< 10 g/dL	24	6		
10–12 g/dL	24	3	3.9	0.13
< 12 g/dL	28	1		
Creatinine				
> 2 mg/dL	9	1		
1.5–2 mg/dL	7	5	12.36	0.002
< 1.5 mg/dL	60	4		
C-reactive protein				
> 15 mg/L	26	3	0.8	0.65
< 15 mg/L	50	7		

Table 8. Relation of type and site of valve affected, NYHA functional status and causal micro-organism to clinical outcome.

Parameter	Patients discharged alive (n = 76)	Patients died (n = 10)	χ^2	p
Native valve IE	44	4	1.97	0.32
Prosthetic valve IE	32	6		
Valve affected				
Mitral	33	4		
Aortic	34	6	0.7	0.59
Tricuspid	5	0		
NYHA class				
IV	16	5		
III	22	1	4.51	0.21
II	13	1		
I	25	3		
Etiology				
Staphylococci	27	4		
Streptococci and Gram-negative	39*	3	0.6	0.6
Negative blood cultures	20	3		

*Including 1 case of fungal IE; IE — infective endocarditis

ture, leukocytosis and impaired renal function but not CRP) were significantly related to mortality (Table 7). There was no definite statistical relation between micro organisms isolated in blood cultures and in hospital outcome (Table 8).

Discussion

Infective endocarditis remains in the 21st century a not uncommon cause of hospitalization with a relevant mortality rate [5, 13].

Our study evaluated a selected group of subjects suffering from severe active clinical disease who had been referred to a tertiary heart surgery center for surgical treatment.

The average age of patients was 59.5 ± 16 years, similar to that reported recently by the International Collaboration on Endocarditis-Prospective Cohort Study [9]. Although NVE is significantly more frequent than PVE [3], the relatively higher percentage of PVE reported in our study accords with investigations from surgical centers, since medical treatment is rarely effective in PVE [14, 15]. Intravenous drug use is a high risk condition for IE. However, less than 5% of our patients were drug addicts. Since antibiotic treatment is often effective in these patients, a low referral for surgery may explain this finding.

Staphylococci were the more frequent etiological agents, again agreeing with previous investigations [16, 17]. Due to the limited number of events we were not able to demonstrate a statistical relationship between etiological agent and prognosis. However, of the ten patients who died during hospitalization, four had positive blood cultures for staphylococcus aureus, while a staphylococcus aureus infection was found only in 17% of surviving patients.

Diagnosis of culture negative endocarditis was made in 24% of patients, a percentage similar to other surgical series [3–9]. Culture negative endocarditis in our study was more frequent in patients with NVE mainly referred from peripheral hospitals, where a large spectrum empiric antibiotic therapy had been administered before definite diagnosis. Since all patients had echocardiographic and, more relevantly, surgical, demonstrations of endocarditis, our data supports the hypothesis that inappropriate antibiotic treatment is the main factor responsible for negative blood cultures [18, 19].

Netzer et al. [3] reported 15% hospital mortality in patients with IE. Similar results were reported in other investigations [13]. Overall hospital mortality has been 17.7% in the International Collaboration on Endocarditis-Prospective Cohort Study [9]. In the present study, overall hospital mortality has been 11.6% (and 12.5% when patients with pacemaker endocarditis were excluded from the analysis) with a higher survival rate compared to that previously reported from medical institutions [3]. Several demographic and clinical factors have been associated with adverse outcome in patients with active IE [3, 10]. Heterogeneity of examined populations, long enrolment periods often lasting more than ten years, and a prevalence of studies from 'medical' institutions may be responsible for the wide difference between hospital and long term mortality reported in literature. Advanced age, severity of hemodynamic impairment and of septic state are significantly related to clinical outcome in the patients included in our study.

The anatomical site of the infectious process and its diffusion to paravalvular tissues, the involvement of a native or prosthetic valve, and the degree of valve regurgitation, did not affect short-term outcome.

Hospital mortality was significantly higher in patients with PVE in comparison to NVE in studies from medical institutions [3, 20, 21]. The usefulness of surgical treatment in patients with PVE is supported by the results of the present investigation in which hospital survival rates did not differ between PVE and NVE.

Higher mortality was found in patients with lower LVEF. Survival, at variance with previous investigations [3, 9, 10], was not related to functional impairment expressed as NYHA class at admission. Surgical treatment in patients with severe acute hemodynamic overload may prevent the development of irreversible evolution leading to cardiogenic shock and contribute to lower in-hospital mortality. In patients with active IE, evidence of LV dysfunction may more accurately predict an adverse outcome than clinical evaluation of functional status.

Age is associated with increased mortality, mainly due to the high prevalence of severe comorbidities. Parameters easily measurable at hospital admission may help to identify a group of patients at higher risk of death. Fever, elevated WBC ($> 15{,}000\ mm^3$) and serum creatinine levels above 1.5 mg/dL at hospital admission were significantly associated with an increased risk of hospital mortality. Patients who died had a heart rate significantly higher in comparison to patients discharged alive. Similar results were reported in the study by Wallace et al. [10]. The relation between an impaired renal function and a poor prognosis in IE has been reported by other authors [3, 22]. Different pathophysiological factors have been hypothesized (hemodynamic changes, immune complex glomerular damage, antibiotic toxicity) [23, 24]. Results from the present investigation suggest that even small changes in renal function have negative prognostic values, and these may be related to the severity of septic process and of consequent intrarenal functional hemodynamic changes. The different clinical and laboratory data suggesting a severe septic condition (fever, elevated WBC, elevated CRP and decreased albumin concentration) with a poor prognosis reported in the study by Wallace et al. [10] is in agreement with this hypothesis.

Limitations of the study

Patients included in this study were referred to a single tertiary heart surgery center and therefore are not representative of the overall IE population. Few investigations however have evaluated the clinical characteristics of patients with active IE referred for surgical treatment and their relation to hospital mortality. An easy clinical and instrumental approach may allow the identification of high risk patients. Future investigations are needed to evaluate if more sensitive markers may improve the capability to detect high risk patients, in whom a more aggressive surgical approach may contribute to a reduction in mortality.

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